Research Paper

A urinalysis-based study of buprenorphine and non-prescription opioid use among patients on buprenorphine maintenance

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ABSTRACT

Objectives: To understand the pattern of use of opioid-substitution therapy (OST) and opioid abuse among patients on buprenorphine maintenance using urinalysis. **Materials and Methods:** The study was conducted at a tertiary care de-addiction center. We reviewed the laboratory record of all consecutive urine samples sent for drug analysis over a period of 1 year. In all, 179 consecutive urine samples were included in the analysis. The chi-square test was used to compare opioid abuse among those testing positive and negative for buprenorphine on urinalysis. Additionally, in order to assess the potential impact of the prescribed induction and maximum dose of buprenorphine on the findings, we carried out the independent-samples t test. Level of statistical significance was kept at $P<0.05$ for all the tests. **Results:** Urinalysis failed to detect buprenorphine in 44.7% of the samples. Rate of detection of dextropropoxyphene was significantly higher among buprenorphine-negative samples ($P<0.005$). The prescribed induction dose of buprenorphine was significantly lower among those testing positive for heroin. This was found for both buprenorphine-positive ($P<0.005$) as well as buprenorphine-negative samples ($P<0.005$). **Conclusions:** These findings support the routine use of urine drug screening among individuals on OST.

Key words: Buprenorphine, opiate substitution therapy, urinalysis

INTRODUCTION

Opioid dependence adversely impacts personal health and economic productivity and is associated with many social and legal problems. There is high chance of relapse after treatment for opioid addiction. As part of harm minimization, opioid substitution therapy (OST) is started for such people. Buprenorphine has been established as a safe and cost-effective long-term alternative to methadone in substitution therapy for opioid dependence. It has shown benefits similar to those of methadone in retaining patients in treatment and improving quality of life and overall health status.[1] However, concerns have been expressed about the compliance with treatment and diversion of the prescription buprenorphine.[2–4] Also, continued non-prescription opioid use has been documented among those on OST with buprenorphine.

The reliability of self-report about non-prescription drug use and compliance with prescribed buprenorphine among opioid abusers remains debatable.[5] It has been recommended that the OST be corroborated and monitored using objective measures

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such as urine drug screening.[6] Use of urinalysis findings when combined with self-report could provide important insights into the pattern of OST use and non-prescription opioid abuse among patients on buprenorphine therapy. Also, it provides objective evidence of the compliance with the prescribed medication.

International guidelines on buprenorphine prescription recommend routine use of some objective method to validate self-report of drug use pattern. Urine drug screening is the most commonly used and the most cost-effective method for this purpose.[7] The guidelines for use of buprenorphine in India are in accordance with the international recommendations. However, use of routine urine drug screening to ensure compliance is not recommended in these Indian guidelines.[8] Lack of resources and technical expertise are possible reasons for this.

The current study aims at understanding the pattern of use of OST and non-prescription opioid use among patients on buprenorphine maintenance. We have used findings from urinalysis as an objective measure for this purpose.

MATERIALS AND METHODS

We reviewed the laboratory records of all urine samples sent for drug analysis over a period of 1 year at a tertiary-care de-addiction center. All cases with buprenorphine prescription for OST during this period were included in the study. All the subjects were being treated as outpatients and were being administered the medication from the treatment center on a biweekly basis.

At this center, urine samples sent for drug evaluation are screened for common drugs of abuse in the region as well as medications prescribed as OST from the center, which include heroin (detected as morphine), buprenorphine, dextropropoxyphene, and benzodiazepines. A supervised urine sample (50 ml) is collected from patients coming for treatment at the de-addiction center. It is then sent to laboratory for analysis. A standardized modified hydrolysis method followed by thin-layer chromatography (TLC) is used for detection of drugs in the urine.[9,10] The detection limit for urinalysis in the laboratory is 0.5 μg/ml for morphine (heroin) and dextropropoxyphene, 0.2 μg/ml for benzodiazepines, and 1.0 μg/ml for buprenorphine.

Data analysis was carried out using SPSS® version 17. The pattern of prescription buprenorphine use and non-prescription opioid use was assessed using frequency distribution. We used the chi-square test to compare non-prescription opioid use among those testing positive and negative for buprenorphine on urinalysis. Additionally, in order to assess the potential impact of the prescribed induction and maximum dose of buprenorphine on the findings, we carried out the independent-samples *t* test.

Conditions of anonymity and confidentiality, as recommended in the institute's ethical guidelines, were strictly adhered to during the study.

RESULTS

A total of 179 consecutive urine samples received over a 1-year period were included in the study. The sociodemographic profile of the study sample and the dose of buprenorphine during the induction and maintenance phases is presented in Table 1.

Buprenorphine was detected in 99 (55.3%) of the samples. Heroin and dextropropoxyphene were detected in 10 (5.6%) and 14 (7.8%) of the samples, respectively. Hence, the rate of non-prescription opioid use was 13.4% [Table 2; Figure 1]. The rate of detection of dextropropoxyphene was significantly higher among buprenorphine-negative samples (chi-square 14.25, df=1; $P<0.005$). The proportion of urine samples testing positive for heroin was similar in buprenorphine-positive samples and in buprenorphine-negative samples (chi-square 0.08, df= 1; $P=0.76$).

The induction dose of buprenorphine was significantly lower among those testing positive for heroin than in those testing negative. This was found for both buprenorphine-positive (n=37; mean dose 2.11±0.78 mg/day *vs* 6.11±5.38 mg/day; $t=-6.94$, $P<0.005$) as well as buprenorphine-negative samples (n=26; mean dose 1.77±0.76 mg/day *vs* 6.17±5.49 mg/day; $t=-5.09$, $P<0.005$) [Table 3].

However, no such difference was observed for the maximum dose of prescription buprenorphine ($t=-3.435$, $P=0.74$ and $t=-0.214$, $P=0.847$ for buprenorphine-positive and buprenorphine-negative urinalysis, respectively). Similarly, no difference was observed for prescribed dose of buprenorphine among dextropropoxyphene-positive ($t=-0.19$, $P=.85$) and dextropropoxyphene-negative ($t=1.34$, $P=.18$) urine samples among urine samples testing positive for buprenorphine.

Table 1: Sociodemographic profile and buprenorphine prescription dose for the study sample (n=179)

Age	38.6±10.35 years
Gender	
Males	179 (100%)
Mean induction-phase buprenorphine dose	4.04 mg (range: 2–6 mg)
Mean maintenance-phase buprenorphine dose	7.89 mg (range: 6–14 mg)

Table 2: Urinalysis findings for opioid use for buprenorphine-prescribed opioid-dependent subjects

Total number of urine samples (n) = 179			
Positive for BPN 99/179 (55.3%)		Negative for BPN 80/179 (44.7%)	
Positive for non-BPN opioids 5/99 (5%)		Positive for non-BPN opioids 19/80 (23.7%)	
Morphine	Dextropropoxyphene	Morphine	Dextropropoxyphene
4/99 (4%)	1/99 (1%)	6/80 (7.5%)	13/80 (16.2%)

BPN: Buprenorphine. Morphine is the biochemical indicator of use of heroin

Table 3: Average induction daily dose of buprenorphine for buprenorphine-positive and buprenorphine-negative urine samples

	Morphine	Mean ± SD (mg/day)	
Induction dose of BPN for BPN- positive urine samples	Positive	2.11 ± 0.78	t=−6.94, P<0.005
	Negative	6.11 ± 5.38	
Induction dose of BPN for BPN- negative urine samples	Positive	1.77 ± 0.76	t=−5.09, P<0.005
	Negative	6.17 ± 5.49	

BPN: Buprenorphine. Morphine is the biochemical indicator of use of heroin

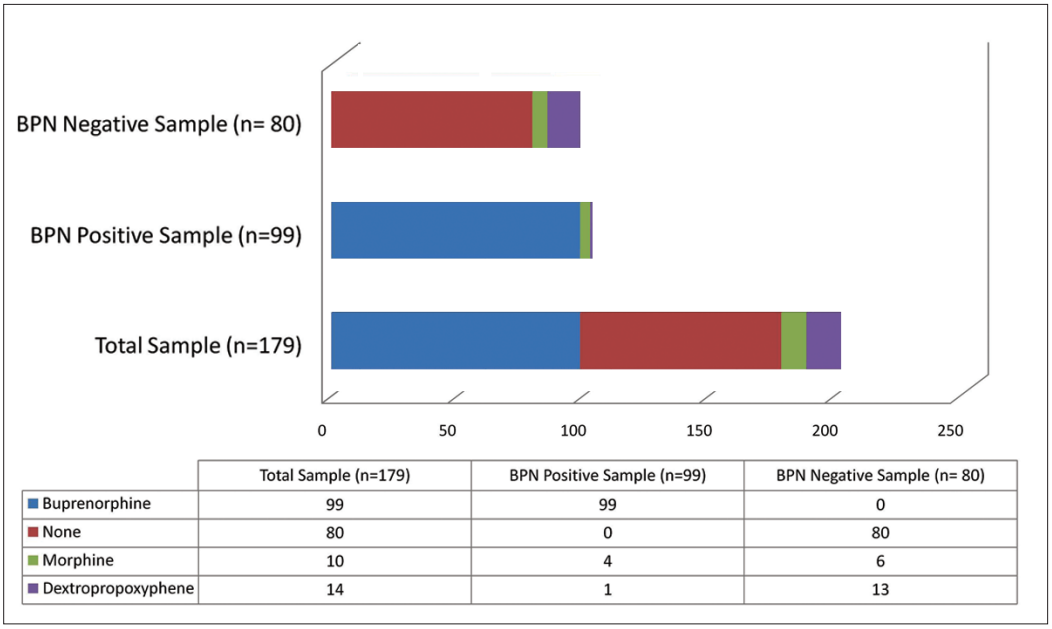

Figure 1: Findings of urinalysis for the total sample, buprenorphine-positive samples, and buprenorphine-negative samples

Also, no differences were observed for prescribed dose of buprenorphine among dextropropoxyphene-positive (t=0.076, P=.94) and dextropropoxyphene-negative (t=1.08, P=.32) urine samples among urine samples testing negative for buprenorphine.

The independent-samples t test failed to find any significant difference between the dose (induction dose as well as maximum dose) of the prescribed buprenorphine and buprenorphine urinalysis status (n=37, t=−0.032, P=0.974; n=26, t=0.641, P=0.524).

DISCUSSION

The current study aimed at understanding the pattern of use of OST and non-prescription opioid use among patients on buprenorphine maintenance. We used findings from urinalysis as an objective indicator for this purpose.

A total of 179 consecutive urinalysis qualified for inclusion in the study. The rate of non-prescription opioid use was 13.4% in the current study. The rate of non-prescription opioid use

among individuals on buprenorphine therapy has been found to vary across studies. It was found to be around 20% in a comparative study of buprenorphine and methadone.[11] Another study by Gerra *et al.* reported it to be around 21%.[12]

All the samples in the current study were from opioid-dependent patients on OST with buprenorphine. However, urinalysis failed to detect buprenorphine in 44.7% of the samples. This noncompliance rate is much higher than the usually observed rate of 30%.[13] This suggests a significant proportion of the individuals were not using the prescribed buprenorphine. Diversion of the prescribed buprenorphine is a possible explanation for this finding. Such diversion of prescription buprenorphine has been reported from different countries, including Australia, England, Finland, France, Ireland, New Zealand, and Scotland.[4]

It is likely that some of those testing positive for dextropropoxyphene (with or without their sample being buprenorphine-positive) might be using dextropropoxyphene in addition to the buprenorphine they were receiving through the OST program. Reports of such 'doctor shopping' behavior among opioid abusers have come from other settings as well.[14] There could be different explanations for such behavior. To begin with, lack of difference in the prescribed dose of buprenorphine among those testing positive and negative for dextropropoxyphene makes the possibility of inadequate dose of prescribed buprenorphine unlikely. However, the stringent requirements of regular follow-up for buprenorphine (daily to twice weekly) might drive these individuals to ration their buprenorphine supply, substituting it in part with dextropropoxyphene. The possibility of diversion cannot be ruled out. Some of those registered with buprenorphine OST might be diverting it, while using dextropropoxyphene themselves. This is a likely explanation for those testing positive for dextropropoxyphene and negative for buprenorphine. The high street value and restricted availability of buprenorphine in the open market makes it a likely candidate for diversion.

Different patterns of treatment non-adherence to buprenorphine prescribed as OST have been observed. These include: (a) diversion to the black market, (b) non-adherence to prescriber's recommendations about the dose to be used, (c) concurrent use of other drugs or alcohol, and (d) unsanctioned administration of buprenorphine (by injection or sniffing).[18] Two of these possibilities, (b) and (c), are supported by the urinalysis findings of the current study. The possibility of diversion to the black market and injecting use could be confirmed through focus-group discussions (FGD) and key informant interviews (KII) with the service users.

Use of an inadequate dose of buprenorphine, especially during the early phases of therapy, is a likely cause of continued use of heroin by opioid abusers. This was observed in the current study, where the induction dose of prescribed buprenorphine was significantly lower among the heroin-positive urine samples. This was observed for those concomitantly testing positive for buprenorphine as well those testing negative for buprenorphine. Gerra *et al.* found high doses of buprenorphine to be more effective than low doses in reducing non-prescription opioid use (f=9.7, $P<0.05$).[12] Also buprenorphine-maintained patients who showed morphine-positive urines had significantly lower doses than those with negative urine screen findings (7.7±0.6 mg/day *vs* 11.3±0.5 mg/day; $t=2.53$, $P<0.05$).[15] In the current study, the induction dose of buprenorphine was significantly lower among morphine-positive as well as buprenorphine-positive urine samples (mean dose 2.11±0.78 mg/day *vs* 6.11±5.38 mg/day; $t=-6.94$, $P<0.005$). Similarly, the induction dose of buprenorphine was significantly lower among morphine-positive but buprenorphine-negative urine samples (mean dose 1.77±0.76 mg/day *vs* 6.17±5.49 mg/day; $t=-5.09$, $P<0.005$).

While some of these under-prescribed individuals may have used heroin as a 'top-up,' others may have discontinued using buprenorphine because of inadequate satisfaction of drug hunger and poor withdrawal management. Inadequate dosing of buprenorphine is a common reason for noncompliance and continued non-prescription opioid use.[15]

While use of low doses of buprenorphine at induction has been associated with poor retention in treatment,[16] rapid up-titration of buprenorphine has been found to improve compliance.[17] Prescription of an adequate dose of buprenorphine has been found to protect against doctor-shopping behavior among opioid abusers.[15] The high ceiling effect for opioid agonist activity with buprenorphine makes it relatively safer in high doses.[18] Prescribers must be aware of this fact and should not under-prescribe. However, prescribers should also be alert to the possibility fatal accidents due to excessive dose of buprenorphine as a result of intravenous misuse or concomitant use of other sedative drugs such as benzodiazepines, which is always a possibility in this group.[19]

OST using buprenorphine–naloxone has been found to be safe and effective, with limited diversion rates.[20,21] This could be an alternative to the use of plain buprenorphine for OST.

The use of urine drug screening in the current study has helped us understand the pattern of use of prescription buprenorphine as well as non-prescribed opioids (including illicit heroin) among those using OST. The reliability of self-report about non-prescription drug use and compliance with prescribed buprenorphine has been, and remains, debatable.[5] International guidelines recommend routine use of some objective method to validate self-report of the service users regarding the drug use patterns.[22] Urine drug screening is the most commonly used and generally most cost-effective method for this

purpose.[23] The findings from the current study also support the routine use of some objective measure to corroborate self-reported drug use by those on OST. Though Indian guidelines on the use of buprenorphine as OST are in accordance with the international recommendations, use of routine urine drug screening to ensure compliance is not recommended in these guidelines.[8] This could be due to lack of resources and technical expertise in the country. However, there is a need to include routine urine drug analysis as an integral component of the OST program. This would help in improving monitoring and thus allow timely intervention.

The current study made use of the urinalysis findings. It did not explore the perspectives of the service users on the issues. It would be informative to explore these issues using FGD and KII among those on OST.

CONCLUSIONS

The findings from the current study provide important insights into the pattern of use of OST as well as that of non-prescribed opioids (including illicit heroin) among individuals on buprenorphine therapy. These findings support routine use of urine drug screening among individuals on OST.

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